The Emergence of Radioimmunoscintigraphy for Prostate Cancer

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The ability to label tissue-specific antibodies has long been of interest for improving detection and guidance for therapeutic applications. The most studied target for prostate cancer is the prostate-specific membrane antigen, which is upregulated in prostate cancer, hormone-refractive disease, and prostate cancer metastases. Investigations using radioimmunoscintigraphy with the radiolabeled 7E11 antibody capromab pendetide have significantly improved sensitivity for prostate cancer detection compared with standard cross-sectional imaging, based on tissue confirmation of pathologic results. Over the past 5 years, significantly greater image resolution from improved camera technology and the use of co-registration to fuse functional and anatomic (computerized tomography and magnetic resonance imaging) images have dramatically enhanced prostate cancer localization. Outcomes data from several sources have spurred a resurgence in interest in this imaging modality.
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Despite significant advances in the management of prostate cancer over the past 15 years, the most common solid tumor in men remains a major clinical problem, with more than 230,000 new cases and a mortality rate exceeding 30,000 men per year in the United States.[1] Progress clearly has been achieved in managing advanced prostate cancer with the use of hormonal therapy, either temporarily or permanently, earlier in the disease process. Progress has

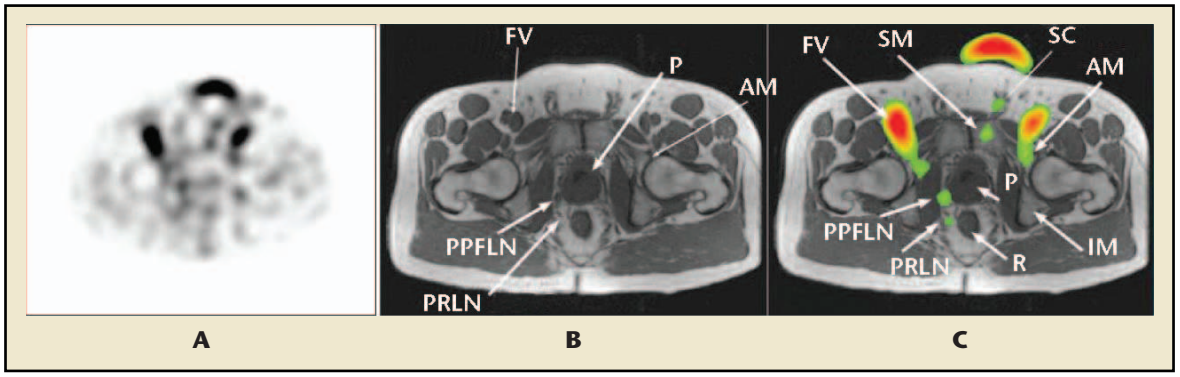


Figure 1. *Physiologic, anatomic, and fused images, showing a suggestion of increased activity on the ProstaScint (physiologic) scan* (A) *and very small periprostatic (PPFLN) and perirectal (PRLN) lymph nodes that do not meet the size criteria for malignancy on the computerized tomography (anatomic) scan* (B). C. *The fused image demonstrates increased signal intensity in lymph node structures separate from vascular structures and bone marrow. Note the signal in the blood pool of the male genital system external to the body and in the spermatic cord (SC). FV, femoral vein; R, rectum; P, prostate; AM, acetabular marrow; SM, symphysis pubis; IM, iliac marrow. Courtesy of Michael K. Haseman, MD, Sacramento, CA.*

also been made in managing hormone-refractory disease with the introduction of taxane-based chemotherapy. This therapy, for the first time, has provided the oncologist with an effective treatment that has a limited but real survival advantage in the terminal stages of disease.

Determination of the extent of disease, however, continues to be a major challenge for selecting appropriate treatment options, detecting disease after suspected recurrence, and monitoring the effects of intervention. Physicians face these diagnostic and treatment dilemmas whether the prostate cancer is in its initial or advanced stages. Disease stage can be predicted to some extent from accumulated clinical information on pathologic grade and tumor markers such as prostate-specific antigen (PSA).[2,3] Clinical nomograms are useful for determining local extension or seminal vesicle involvement, because this information is based on actual pathologic evaluation of the entire prostate gland and adjacent tissue. However, the prediction of lymph node metastasis is less accurate because, in the vast majority of cases, tissue evaluation is based on biopsies from a limited sample of the area of possible lymphatic spread. The underestimation of nodal disease is emphasized by the finding of perirectal lymph nodes with prostate cancer in 4.5% of patients who underwent abdominoperineal resection for colorectal carcinoma (Figure 1).[4] In 1990, Saitoh and colleagues[5] conducted a study of 753 autopsy prostatic cancer cases and found that prostate cancer frequently involves lymph nodes outside the pelvis itself, the most common location being the periaortic lymph nodes. In a subgroup of patients who had only lymph node metastatic involvement, the periaortic lymph nodes were more involved than the pelvic lymph nodes themselves. Although there has been some improvement in detection of positive lymph nodes with extended lymph node dissection, the 39% (4-year) and 43% (5-year) progression-free rates portend a greater extent of the disease.[6,7] Lymph node metastasis is underestimated even in the low-risk prostate cancer population.[7]

Current Status of Imaging

Conventional cross-sectional imaging with computerized tomography (CT) and magnetic resonance imaging (MRI) to detect prostate cancer and lymph node metastasis has well-recognized limitations. Both CT and MRI use size criteria for detecting metastases in lymph nodes (Figure 2), but the use of size criteria has a low sensitivity. Several reports demonstrate that the sensitivity of CT for lymph node metastases using size criteria ranges from 25% to 78%, with a specificity of 77% to 98%.[8-12] Claims of CT sensitivity have been accompanied by very few tissue confirmation studies, and one telling report on lymph node metastasis with tissue confirmation demonstrated a sensitivity of only 4% in intermediate- to high-risk prostate cancer patients.[12] When adenopathy is detected, CT cannot distinguish between inflammatory and malignant infiltration.[13] Consequently, CT is best reserved for patients with clinical stage T3 or T4 disease, for radiotherapy pretreatment planning, or for conformal image co-registration.[14]

Previous reports have found whole-body MRI to be more sensitive and specific than CT in evaluating patients for metastatic disease, but MRI suffers from the same size criteria limitations as CT. MRI may be useful as an adjunct to skeletal scintigraphy. However, the development of new MRI contrast agents seems to have enhanced the utility of this modality. In particular, ultrasmall superparamagnetic iron oxide particles significantly

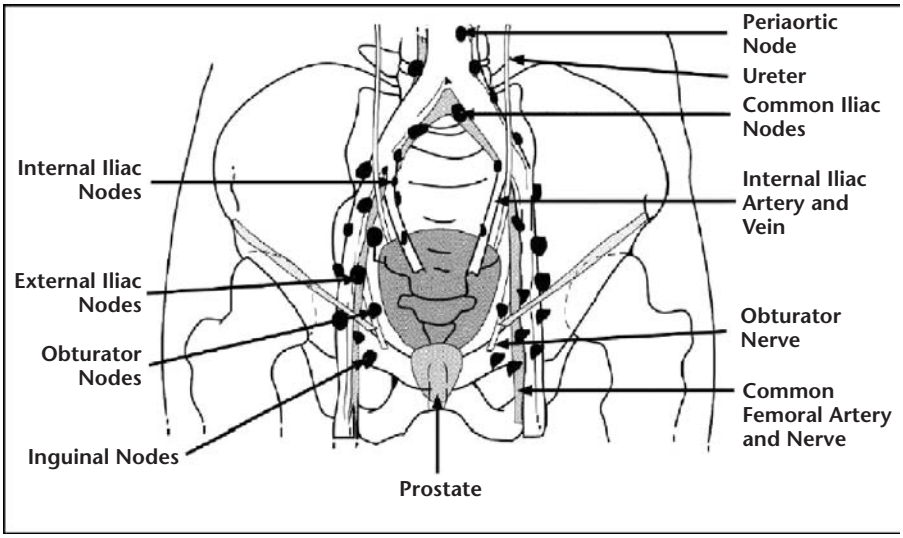


Figure 2. *Schematic depiction of the most common areas of pelvic lymph node metastasis from prostate cancer.*

improved detection of even very small lymph nodes compared with MRI alone.[15] Addition of this contrast agent changes evaluation of lymph nodes by size to evaluation by functional activity. Unfortunately, this imaging agent is not presently available for general use in the United States.

Functional tumor activity is also the basis for positron emission tomography (PET). PET measures metabolism of a radiolabeled analog in tissue, and the higher metabolic rate of malignancies registers an increased signal. The most commonly used radiotracer for PET is ^{18}F-fluoro-2-deoxyglucose, but this analog is not particularly useful in evaluating prostate cancer.[16] Also, PET cannot differentiate between tumor and hyperplasia and is less sensitive than scintigraphy for osseous metastases.[16] Although some newer analogs may be more useful for prostate cancer, the current use of PET for prostate cancer patients is limited, most likely due to the generally low glycolytic rate in prostate cancer and its metastases.[17]

The Evolution of Radioimmunoscintigraphy

One of the most promising approaches for imaging cancer is the increasing use of radioimmunoscintigraphy. Distinctly different from anatomic imaging, with its size criteria, radioimmunoscintigraphy detects signal from a radiolabeled antibody that recognizes prostate tissue. The most commonly used antigen for recognition is prostate-specific membrane antigen (PSMA), which is expressed in prostate cells and upregulated in higher-grade lesions, in androgen-insensitive disease, and in metastatic deposits.[18-22] The most intensively studied monoclonal antibody conjugate to PSMA is 7E11, capromab pendetide (ProstaScint®; Cytogen Corporation, Princeton, NJ), a 100-kd type II transmembrane glycoprotein that recognizes an intracellular epitope.[23] Several other candidates with external epitopes have been evaluated, but none have been approved for general use.[24] Despite controversy about whether this antibody recognizes live tissue, capromab pendetide has been shown to bind to live cells, and several studies have shown a high correlation between pathologic specimens and scan results.[12,25-27]

The clinical trial submitted to the US Food and Drug Administration for approval demonstrated a sensitivity of ProstaScint scan of 63% (compared with 4% for CT and 15% for MRI) and a negative predictive value of 92% with tissue confirmation of scan results.[12] The ProstaScint scan, however, was not widely adopted at that time because of erratic scan results at other clinical sites. These variable-accuracy reports resulted from differences in the camera technology used for image acquisition and from lack of experienced nuclear medicine physicians to perform and interpret the scans. However, major advances in image acquisition and the advent of image co-registration are significantly enhancing and standardizing the accuracy of prostate cancer detection.

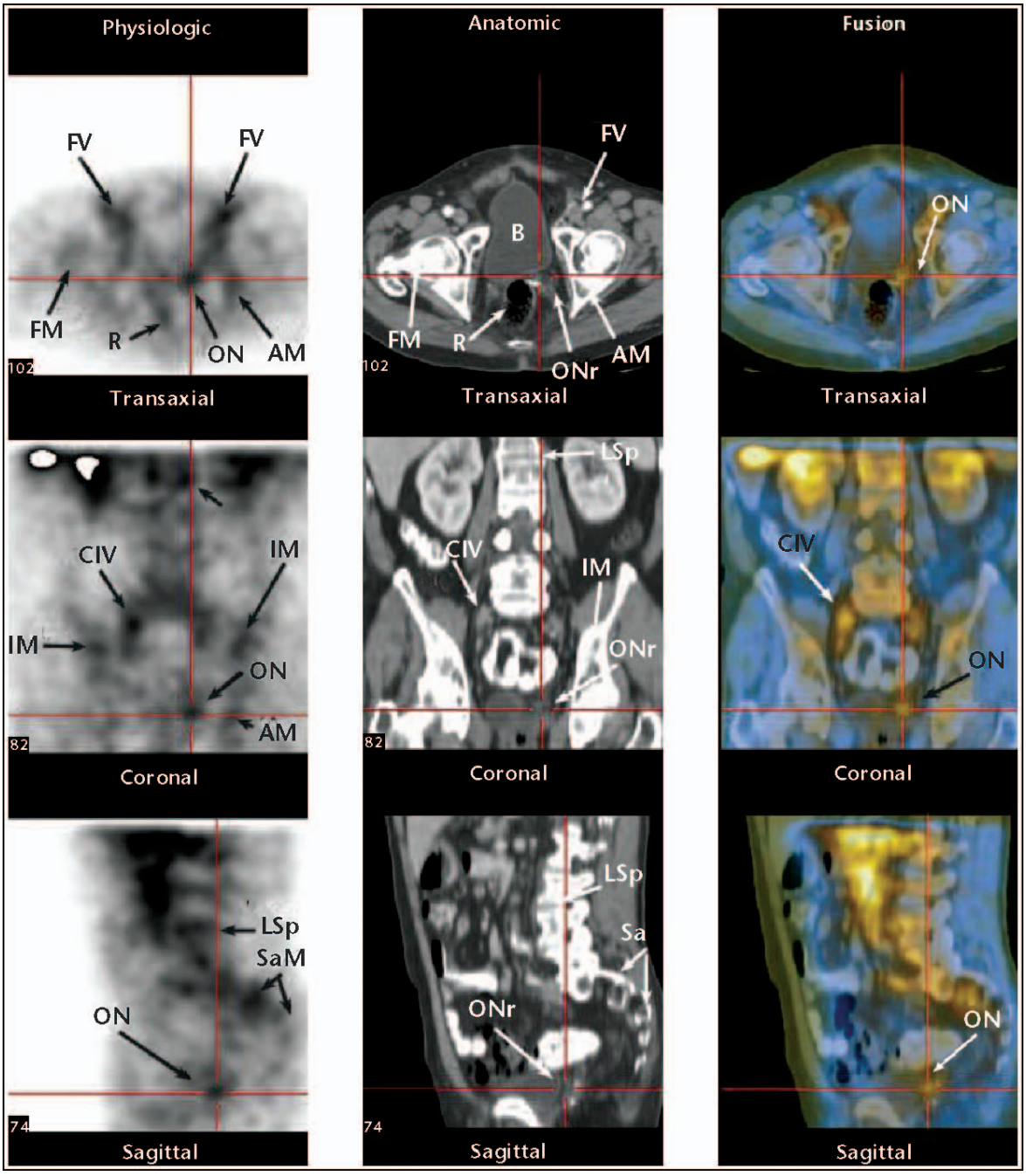
The functional image provided by radioimmunoscintigraphy has now been combined with anatomic imaging such as CT or MRI. The fusion of these images is a direct outgrowth of the realization that PET and CT fusion enhances resolution for detecting other tumor types. The use of dual-head gamma cameras to co-register the functional single-photon emission tomography (SPECT) and an anatomic image has made a dramatic difference in prostate cancer detection with the 7E11 radioimmunoconjugate.[27-29] Localization accuracy has doubled, and tissue confirmation of scan results now demonstrates an accuracy of 83% with fused images.[28,29] The improvement in

The functional image provided by radioimmunoscintigraphy has now been combined with anatomic imaging such as CT or MRI.

image quality and tumor localization shows that imaging with capromab pendetide has evolved from its earlier stages to much more standardized, reproducible images with much greater resolution (Figure 3).

In addition to the improvement in image acquisition and interpretation, the emergence of clinical outcomes data related to PSMA and capromab pendetide scan results strongly supports the use of this immunoconjugate.

Figure 3. *Physiologic, anatomic, and fused images in transaxial* (top row), *coronal* (middle row), *and sagittal* (bottom row) *planes. All image sets are triangulated on the obturator node (ON) seen on the ProstaScint (physiologic) scan (images on the left). Lymph nodes not clearly seen on the computerized tomography (anatomic) scan (images in the middle) are designated as obturator node region (ONr). Note the benign uptake in the degenerative lumbar spine (LSp), acetabular marrow (AM), bladder (B), femoral veins (FV), femoral marrow (FM), iliac marrow (IM), and rectum (R). CIV, common iliac vein; SaM, sacral marrow. Courtesy of Leone Gordon, MD, Medical University of South Carolina, Charleston, SC.*



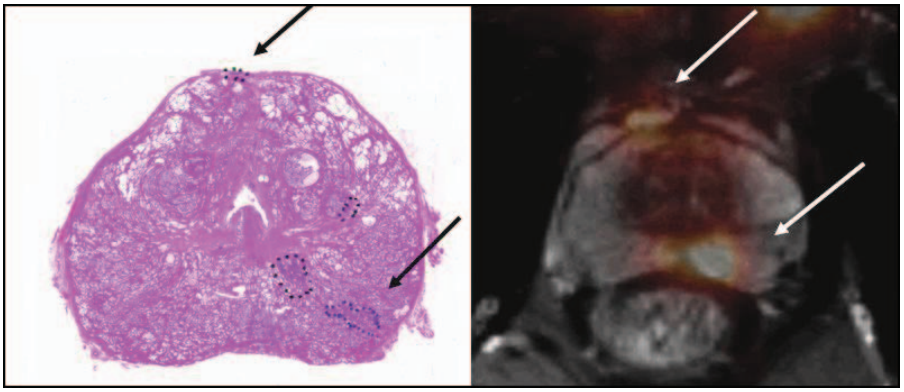


Figure 4. *Fused ProstaScint and MRI images* (right) *demonstrating 2 areas of focal activity (white arrows) that correspond to step-sectioned pathologic presence of prostate cancer (black arrows,* left*). Circled areas without arrows represent inflammation. Courtesy of Rodney Ellis, MD, and Bruce Sodee, Case Western Reserve University, Cleveland, OH.*

It is now known that patients with prostate cancer that overexpresses PSMA in the prostate gland have twice the recurrence rate and a shorter time to recurrence than those with normal PSMA expression in the gland.[30] The much clearer fused scans have been correlated with step-sectioned evaluation of prostate specimens to demonstrate an 80% overall accuracy, with sensitivity of 79%, specificity of 80%, positive predictive value of 68%, and negative predictive value of 88% for detection of cancer within the prostate gland (Figure 4).[31]

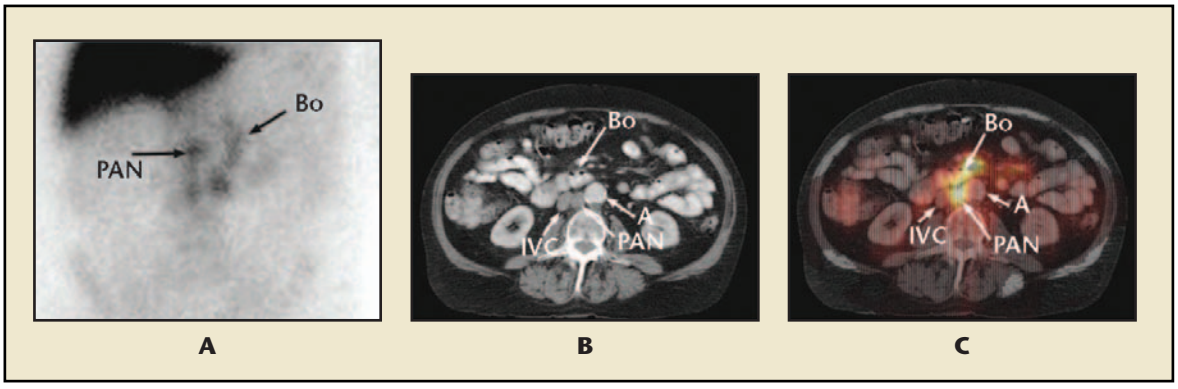
This preliminary study was used to guide focal brachytherapy for intermediate- to high-risk prostate cancer patients, for whom the treatment field was altered on the basis of increased signal in areas of the prostate on the image.[32] The 7-year follow-up data for 239 patients demonstrated superior results across all risk categories compared with the 5-year meta-analysis of brachytherapy patients (96% vs 87% for low risk, 87% vs 74% for intermediate risk, and 73% vs 50% for high risk).[33] Furthermore, patients with positive scan results outside the pelvis showed a 9-fold increase in biochemical disease recurrence, regardless of risk category (Figure 5).

These data suggest that the scan results can be used both to predict better outcomes on the basis of the absence of distant signal intensity and to direct increased dosimetry to focal areas of increased uptake within the prostate gland. These results have stimulated the use of focal image guidance to deliver intensity-modulated external beam radiotherapy (EBRT), with encouraging results.[34] On the basis of these findings, focal image-guided cryotherapy for localized prostate cancer is now underway at several sites.

Imaging in Recurrent Disease

The question of disease extent and location is also paramount for patients with a rising PSA level after prostatectomy who are being considered for salvage radiation therapy. The same story of variable reports in studies from the era before fusion and improved image acquisition for newly diagnosed patients has been repeated for post-prostatectomy patients undergoing salvage EBRT. Reports evaluating the use of capromab pendetide to select patients for radiotherapy have shown mixed results, with some authors demonstrating a durable complete biochemical response to EBRT over a nearly 5-year period and others claiming there is no advantage to using the ProstaScint scan.[35-38] The studies that claimed no advantage used images obtained in the era before dual-head cameras and fused

Figure 5. A. *Periaortic lymph node (PAN) and bowel (Bo) activity detected on radioimmunoscintigraphy. Small periaortic lymph nodes are noted on computerized tomography* **(B)**, *with confirmed high-signal activity on the fused scan* **(C)** *separate from intestinal excretion. A, aorta; IVC, inferior vena cava. Courtesy of Robert McDonald, MD, Fort Myers, FL.*



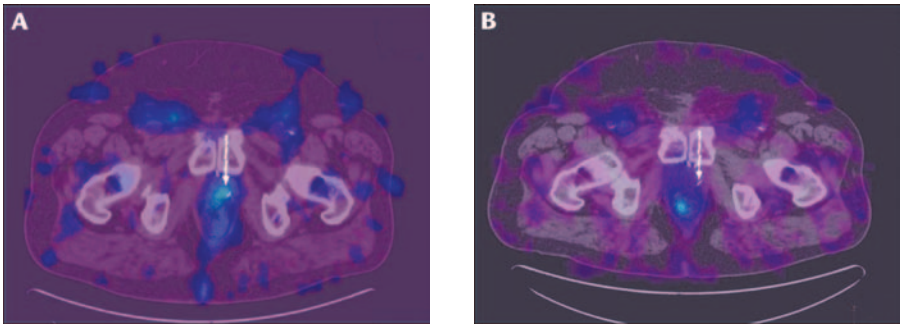


Figure 6. A. *Increased signal intensity (arrow) on fused ProstaScint scan in the prostatic bed of a patient with a rising prostate-specific antigen (PSA) level after PSA nadir at undetectable levels following radical prostatectomy. Note the mild activity in the bowel and bone marrow.* B. *Repeat fused ProstaScint scan in the same patient 6 months after salvage external beam radiotherapy, with now undetectable PSA. The absence of signal in the prostatic bed contrasts with the presence of increased signal in the rectal lumen and bowel. Without scan fusion to align anatomy with the functional study, this scan would have been falsely read as persistently positive. Both images courtesy of Bradley Prestidge, MD, and Yong Bradley, MD, Texas Cancer Clinic, San Antonio, TX.*

images, when image quality varied among institutions depending on the method of image acquisition and the skill of the reader. In the modern era, with fused images from higher-resolution cameras, investigators confirm the value of radioimmunoscintigraphy.[34] These reports suggest that the fused scans will be more suitable for patient selection and for localization for targeted therapy (Figure 6).

Further investigation at Walter Reed Army Medical Center into the use of ProstaScint for patients with a rising PSA who received a scan prior to radiation therapy has produced interesting results for the treatment of locoregional disease. In this study, patients with disease outside the prostatic fossa were more likely to receive whole-pelvis radiation. This group of patients achieved better biochemical control (unpublished data). These preliminary data suggest that with even greater improvements in resolution to delineate regional disease, patients with disease confined to the pelvis who receive extended pelvic irradiation may do better than patients who receive radiation to the prostatic bed only. Furthermore, patients with disease demonstrated to be outside the pelvis will be spared inappropriate treatment, with its attendant expense and possible morbidity.

More recent studies of patients who received scans after increased PSA following local curative therapy with either radiotherapy or prostatectomy are also promising. Investigators at the Medical University of South Carolina (MUSC) recently completed a preliminary retrospective review of 50 ProstaScint scans of patients with persistent or newly rising PSA values following prostatectomy, in a database of 660 patients scanned since 1997. Indications for imaging in this group included biochemical PSA failure following radical prostatectomy or radiation therapy (all types). ProstaScint scans performed before September 2004 were acquired with dual-head camera SPECT, with subsequent patients having co-registration of the SPECT images with high-resolution CT (fused scans). Patients were stratified by published risk categories using PSA, Gleason score, and clinical stage, and by whether or not they received co-registered scans. Of the 50 patients studied, 25 were categorized as high risk, 17 as intermediate risk, and 8 as low risk for disease recurrence, and 32 received fused ProstaScint scans.

In the high-risk group, 16 of 25 patients had fused scans, with 7 scans interpreted as having scintigraphic signal only within the prostatic bed, 4 scans with signal outside the prostatic bed, and 5 scans with no signal activity. Of the 7 patients with prostatic bed activity, 5 received EBRT alone or in combination with androgen ablation and demonstrated a durable undetectable-PSA response; 1 patient, enrolled in a chemotherapy protocol, had a PSA reduction to 0.04 ng/mL; and the remaining patient awaits treatment decision. Of the 4 high-risk patients with signal outside the prostate, 2 patients received EBRT and 24 months of androgen ablation, with a durable PSA decline to 0.1 ng/mL; 1 patient with nodal disease confirmed at surgery who elected observation had a slow PSA doubling time (PSADT) of 23 months; and 1 patient was treated with androgen blockade, with a durable PSA decline to less than 0.1 ng/mL. Of the 5 patients without signal on ProstaScint scan, 3 patients received EBRT without androgen ablation and responded with a durable PSA level of less than 0.5 ng/mL for at least 1 year, 1 patient elected observation and had a PSADT of 5 months, and 1 patient awaits EBRT.

Nine patients in the high-risk group underwent SPECT without fusion, 6 patients with signal only in the prostatic bed and 3 patients with distant signal. Three of the 6 patients with prostatic bed activity received EBRT or androgen ablation alone or in combination and demonstrated a PSA response. The 3 other patients, all with negative surgical margins, received EBRT and androgen ablation and have developed hormone-refractory disease. All 3 patients with signal outside the prostate were treated with androgen blockade and progressed to hormone-refractory disease.

In the intermediate-risk group, 13 of 17 patients had fused ProstaScint scans. Six scans were interpreted

with signal only in the prostatic bed, 1 scan had signal outside the prostate, and 6 scans had no activity. Of the 6 patients with prostatic bed activity only, 4 patients received EBRT alone or in combination with hormonal therapy and experienced a durable undetectable-PSA response, 1 patient elected observation, and 1 patient awaits EBRT therapy. The patient with signal outside the prostate has a rapid PSADT and awaits chemotherapy. Of the 6 patients without signal, 4 patients received EBRT alone or in combination with androgen ablation and had a durable PSA level decrease, 1 patient awaits EBRT treatment, and 1 patient chose observation.

Of the 4 intermediate-risk patients undergoing SPECT without fusion, 1 patient with only prostatic bed activity elected observation and has a slow PSADT, 1 patient had signal distant from the prostate and developed hormone-refractory disease, and 1 of the 2 patients with no signal responded to androgen ablation but the other developed hormone-refractory disease.

The 8 patients in the low-risk category underwent radioimmunoscintigraphy, 3 of them with fused scans that registered signal in the prostatic fossa only. One patient was treated with EBRT and hormonal therapy, with a PSA response; 1 patient elected observation, with a slow PSADT; and 1 patient developed hormone-refractory disease. Of the 5 patients evaluated with SPECT alone, 1 patient with only prostatic bed activity who elected EBRT had a durable PSA response; 2 of 3 patients with distant signal developed hormone-refractory disease, with 1 patient responding to androgen ablation, and the patient with no signal responding to androgen ablation.

All 25 patients in the high-risk group ordinarily would have been candidates for prolonged hormonal therapy. But based on the scans, 6 patients avoided hormonal therapy and underwent only EBRT, with a durable PSA response. None of the 16 patients undergoing fused scans ultimately required long-term hormonal therapy, and none have developed evidence of hormone-refractory disease to date. Without the additional information provided by the ProstaScint scan, these patients likely would have received long-term hormonal therapy based on their high-risk parameters alone. Based on this imaging technology, hormonal therapy was used on a temporary basis in conjunction with EBRT, with subsequent durable PSA responses.

Use of ProstaScint co-registered with CT scan for intermediate-risk patients allowed appropriate treatment selection both for patients with prostatic bed signal and patients with negative signal, with all responding to either EBRT alone or EBRT in combination with short-term hormonal therapy (6 months). Radiolabeled imaging techniques correctly identified 2 patients with metastatic disease.

Radioimmunoscintigraphy with ProstaScint correctly identified localized disease in 4 of 5 patients with low-risk characteristics, all 5 of whom experienced sustained results from EBRT alone or in combination with short-course androgen ablation. These scans also identified a metastatic signal in 3 patients at low risk for metastasis, 2 of whom developed hormone-refractory disease.

Based on these data, the MUSC investigators believe that radioimmunoscintigraphy with ProstaScint, when combined with clinical risk features, provides significantly more information than clinical parameters alone. The use of fused images seems to have an advantage over SPECT scans alone for tumor localization. These encouraging results will be evaluated with a larger patient cohort, but they do suggest that ProstaScint may well be an important factor in an algorithm for treatment of recurrent disease following definitive therapy.

Radioimmunoscintigraphy with ProstaScint, when combined with clinical risk features, provides significantly more information than clinical parameters alone.

Imaging for Salvage Therapy Following Radiation Treatment Failure

Prostate cancer recurrence after radiotherapy presents several challenges for appropriate management. Once again, a crucial component is to identify correctly those patients with persistent localized disease and the potential to benefit from options aimed at curative therapy. In recent years, prostate ablation by cryotherapy has evolved into an accepted treatment option for patients with biochemical failure following radiation therapy.[39] In order to optimize patient selection, the MUSC investigators use an algorithm based on ProstaScint scan results and repeat prostate biopsy to identify patients most appropriate for salvage cryotherapy.

In a recent retrospective review, 24 prostate cancer patients were identified who, since 2003, had undergone ProstaScint imaging fused with CT following biochemical recurrence after radiation therapy. Patients considered for cryotherapy had findings of either radiotracer activity in the prostatic bed or no evidence of activity, along with a positive prostate biopsy to confirm the presence of residual disease. Patients were stratified into 2

clinical risk groups to compare the likelihood of metastatic or local recurrence based on clinical parameters alone. Low risk was defined as T1-T2 stage, Gleason 3 + 4 or less, pretreatment PSA less than 10 ng/mL, PSA nadir of less than 0.5 ng/mL, and PSADT longer than 10 months. The high-risk category included T3-T4 lesions, Gleason 4 + 3 or higher, PSA greater than 10 ng/mL, positive seminal vesicle involvement, PSADT less than 10 months, or failure of PSA to nadir at less than 0.5 ng/mL following radiation therapy.

Of the 24 patients, 21 with negative or prostatic bed activity on ProstaScint scan and a positive prostate biopsy received salvage cryotherapy; 3 patients were excluded from consideration because of signal outside the prostate on the fused scan, leading to a high suspicion of metastatic disease. Prostate biopsy in these 3 patients revealed histology consistent with radiation change in 2 patients and poorly differentiated adenocarcinoma in the third. Thirteen of the 21 patients (62%) receiving cryotherapy treatment demonstrated a durable PSA response of less than 1.5 ng/mL over a median follow-up of 1.4 years. Of the 8 patients who failed to respond to cryotherapy, 7 patients demonstrated poorly differentiated adenocarcinoma on repeat biopsy after therapy, and 1 patient was positive at both seminal vesicles.

Based on clinical data alone, 14 of the 24 patients would have been selected for salvage therapy. Interestingly, 3 of these clinically low-risk patients failed to have a PSA nadir of less than 1.5 ng/mL following cryotherapy and were deemed treatment failures. Another 3 patients who would have been selected for cryotherapy actually demonstrated metastatic signal on ProstaScint scan and were therefore excluded from treatment. In contrast, 5 of the 10 patients thought to have a high clinical risk of metastatic disease but with scans suggestive of local disease only had a durable PSA response after cryotherapy treatment.

In summary, the decision to perform cryosurgery based on clinical data alone was ultimately accurate in 8 of 24 patients (33%). With the use of the fused ProstaScint scan algorithm to select salvage cryotherapy patients, 13 of 21 patients (62%) were identified correctly, with a durable PSA response following treatment. In addition, those patients who failed to respond to salvage cryotherapy demonstrated more aggressive disease on repeat prostate biopsy. These data suggest that the MUSC algorithm combining fused ProstaScint images and biopsy information identified significantly more patients appropriate for salvage cryotherapy than clinical parameters alone. These encouraging results certainly warrant expanded studies to verify the utility of these patient selection criteria to enhance clinical outcomes for a patient population with few choices for salvage therapy.

Conclusion

One must keep in mind that radioimmunoscintigraphy studies conducted before the late 1990s used images obtained in an era before dual-head

Main Points

- The ability to label tissue-specific antibodies has long been of interest for improving detection and guidance for therapeutic applications. The most studied target for prostate cancer is the prostate-specific membrane antigen (PSMA), which is upregulated in prostate cancer, hormone-refractive disease, and prostate cancer metastases.
- Early use of radioimmunoscintigraphy with the radiolabeled 7E11 antibody capromab pendetide (ProstaScint) significantly improved sensitivity for prostate cancer detection compared with standard cross-sectional imaging, based on tissue confirmation of pathologic results.
- Over the past 5 years, significantly greater image resolution from improved camera technology and the use of co-registration to fuse images have dramatically enhanced prostate cancer localization.
- Outcomes data from several sources have spurred a resurgence in interest in radioimmunoscintigraphy. For example, overexpression of PSMA in prostate cancer tissue relates to earlier and faster biochemical recurrence; fused scans provide an 83% accuracy for prostate cancer localization; a midabdominal signal on ProstaScint scan is associated with a 9-fold increased incidence of death from prostate cancer; and 7-year outcomes data from brachytherapy patients with treatment based on fused scan results show a strongly significant difference in biochemical disease-free survival.
- The use of ProstaScint has been expanded to include algorithms for patients with biochemical disease recurrence following prostatectomy and radiotherapy.
- Data are emerging about the value of fused ProstaScint scans in selecting patients for salvage cryotherapy following radiation treatment failure.

cameras and fused images. Image quality varied among institutions, depending on the method of image acquisition and the skill of the reader. In the modern era, with fused images from higher-resolution cameras, investigators have confirmed the value of radioimmunoscintigraphy.[34] The findings suggest that fused scans will be more suitable for patient selection and for localization for targeted therapy, and several sites are now reevaluating the role of immunoscintigraphy as a guide for selecting patients and anatomic targets for therapy. ■

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